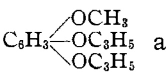
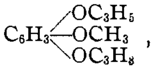
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

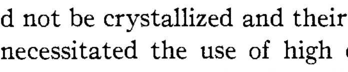
Unsaturated Ethers of Pyrogallol

BY CHARLES D. HURD AND CHARLES I. PARRISH[1]

Since Claisen's original work on the pyrolysis of allyl ethers of phenols extended study has been given to both mono- and dihydric[2] phenols. Pyrogallol derivatives have been allylated in a few instances[3] but not pyrogallol itself. This trihydric phenol, therefore, was studied and its allyl, hexenyl and heptenyl derivatives made.

Pyrogallol allyl triether and the two possible pyrogallol allyl diethers were obtained. The two diethers were not identified but each one was converted to the corresponding methyl diallyl triethers,  $C_6H_3{<}^{OCH_3}_{OC_3H_5}{-}OC_3H_5$ and  $C_6H_3{<}^{OC_3H_5}_{OC_3H_8}{-}OCH_3$, one of which underwent rearrangement smoothly at 200°, whereas the other carbonized extensively. The allyl monoether of pyrogallol was not separated into its two isomers but the reaction with lead acetate pointed to a 4:1 ratio of 3-allyloxycatechol to 2-allyloxyresorcinol. It was assumed that any lead salt would come from the former because of its structural similarity to catechol. The catechol type of dihydric phenol is the one which forms lead salts readily.

The hexenyl and heptenyl derivatives of pyrogallol were very difficult to purify. Being oils, they could not be crystallized and their low vapor pressure necessitated the use of high distillation temperatures, even in a molecular still. Insolubility of the hexenyl triether in alkali was not a safe criterion for the absence of the hexenyl diether and the presence of the latter in the former was indicated by analysis. The hexenyl diethers were not isolable as such from the alkali-soluble fractions for at the temperature of distillation (molecular still) rearrangement ensued, giving rise to dihexenylpyrogallol[4]



$$\left(CH_2{=}CH{-}\underset{C_3H_7}{\underset{|}{CH}}{-}\right)_2C_6H(OH)_3$$

Heptenylpyrogallol, $C_7H_{13}C_6H_2(OH)_3$, and diheptenylpyrogallol were prepared similarly. The former was a solid and the latter an oil. The ethyl triether of the former was prepared by means of ethyl sulfate.

Bactericidal data on the pyrogallol derivatives were obtained through the courtesy of the Parke, Davis and Company Laboratories. The phenol coefficients found toward *Staphylococcus aureus* at 37.5° are listed in Table I. The values for three resorcinol derivatives have been included for purposes of comparison. The dihexenylpyrogallols (I) and (II) were also tested against *Streptococcus hemolyticus* at 37.5°, giving phenol coefficients, respectively, of 110 and 325. In contrast to the relatively high germicidal efficiency toward the *Staph.* and *Strept.* organisms, both of the dihexenylpyrogallols gave phenol coefficients of less than 11 when tested (at 20.5°) against *B. typhosus*.

TABLE I

PHENOL COEFFICIENTS

Pyrogallol allyl monoether	15
Pyrogallol allyl diether (I)	6
Pyrogallol allyl diether (II)	8
Dihexenylpyrogallol (I)	20
Dihexenylpyrogallol (II)	250
Heptenylpyrogallol	120
Diheptenylpyrogallol	20
Resorcinol *n*-propyl monoether[a]	5
Resorcinol *n*-hexyl monoether[a]	125
n-Hexylresorcinol[b]	98

[a] Klarmann, Gatyas and Shternov, THIS JOURNAL, **53**, 3399 (1931). [b] Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926).

Experimental Part

Reagents.—1-Hexene-3-ol, $CH_2{=}CHCHOHC_3H_7$, was prepared in 75% yields from acrolein (50 g. or 0.89 mole) and *n*-propylmagnesium bromide (3.1 moles) by Delaby's method.[5] Delaby used a molar ratio of 1:2 instead of 1:3.4 and obtained a much smaller yield, namely, 40.7%. The $n^{26}\text{D}$ value of 1.4215 confirmed Delaby. Similarly, 1-heptene-3-ol, $n^{24}\text{D}$ 1.4277, was prepared in 55% yield from acrolein and *n*-butylmagnesium bromide, reacting in the molar ratio of 1:1.5. Delaby used the ratio of 1:2 and reported a 35% yield.

These alcohols were converted respectively into 1-bromo-2-hexene[6] and 1-bromo-2-heptene by an adaptation of Kamm and Marvel's[7] procedure for converting allyl

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(1) Parke, Davis and Company Fellow, 1931–1933.

(2) Hurd, Greengard and Pilgrim, THIS JOURNAL, **52**, 1700 (1930); Hahn and Stenner, *Z. physiol. Chem.*, **181**, 88 (1929).

(3) Pyrogallol methyl diether by Mauthner, *J. prakt. Chem.*, **102**, 36 (1921); methyl syringate by Hahn and Wassmuth, *Ber.*, **67**, 696 (1934).

(4) For structure of the analogous hexenylphenol, see Hurd and McNamee, THIS JOURNAL, **54**, 1648 (1932).

(5) Delaby, *Ann. chim.*, [9] **19**, **287** (1923).

(6) The 3-bromo-1-alkenes which might be anticipated are unstable and rearrange spontaneously to 1-bromo-2-alkenes.[4]

(7) Kamm and Marvel, THIS JOURNAL, **42**, 308 (1920).

alcohol to allyl bromide, namely, by reaction with hydrobromic and sulfuric acids: $CH_2{=}CH{-}CHOH{-}R + HBr \longrightarrow BrCH_2{-}CH{=}CHR + H_2O$.

1-Hexene-3-ol (75 g., 0.75 mole) was added slowly to a mixture of 150 cc. (2.3 moles) of 48% hydrobromic acid and 33 cc. (0.6 mole) of concd. sulfuric acid. The whole was stirred for twenty-four hours at 20–25°. The two layers were separated and the aqueous one ether extracted. The combined bromohexene portions were washed with sodium bicarbonate solution, dried over sodium sulfate and distilled. The yield of 1-bromo-2-hexene, n^{26}_{D} 1.4715 (literature, 1.4712), which was collected at 44–46° (14 mm.) was 86 g. (70.5%).

1-Heptene-3-ol (133.5 g., 1.18 moles), 200 cc. of 48% hydrobromic acid and 46 cc. of concd. sulfuric acid were treated similarly. The yield of 1-bromo-2-heptene, b. p. 71–73° (17 mm.), n^{24}_{D} 1.4693, was 170 g., or 81.3% of the theoretical.

Preparation of the Allyl Ethers

Pyrogallol was dissolved in acetone (100–150 cc. for each 0.1 mole of pyrogallol). Somewhat more than the calculated quantity of potassium carbonate was added. Then allyl bromide was added dropwise (about 0.1 mole per hour) through a reflux condenser. The refluxing was maintained for four to six hours. These molar quantities of pyrogallol and allyl bromide were used respectively: for triether 0.1:0.3; for diether 0.2:0.4; for monoether 0.2:0.1.

To work up the products, the mixture was cooled, filtered and the filtrate concentrated on a water-bath. The residue was taken up in benzene in the case of the tri- and diethers and in ethyl ether for the monoether. The benzene solution was washed free of pyrogallol (as evidenced by lack of brown color toward ferric chloride solution). Then it was extracted with 5% sodium hydroxide solution to extract the diether from the triether. About three-fifths as much diether as triether resulted when the 0.1:0.3 ratio of reactants was taken, and about equal quantities of the two ethers were isolated when the 0.2:0.4 ratio was maintained.

Pyrogallol Allyl Triether, $C_6H_3(OC_3H_5)_3$.—The benzene solution was dried, the solvent removed and the residue (11 cc. from 12.6 g. of pyrogallol) distilled in a closed system (two bulbs, the distilling and receiving bulbs, connected in series to an efficient oil pump) at 0.05 mm. and a bath temperature of 125°. The colorless, mobile distillate weighed 10.5 g. or 43% of the theoretical.

Pyrogallol Allyl Diether (I).—The alkaline extract (above) was acidified, extracted with ethyl ether, the ether removed and the 7 cc. of residue twice distilled in the closed system at 0.0005–0.001 mm. and 90–95°. The yield of colorless liquid was 6.1 g.; n^{20}_{D} 1.5345.

When synthesized with the 0.2:0.4 ratio of reactants (thus, from 25.2 g. of pyrogallol) 10 cc. of the triether was separated. The alkali-soluble portion was collected as before but the residue of the diether was fractionated in a Hickman molecular still[8] at 0.040–0.050 mm. and 100°. Several arbitrary fractions were collected whose n^{20}_{D} were taken. Those of similar refractive index were combined and refractionated. Two substances were present. The more volatile fraction (5 g.) was pyrogallol allyl diether (I) for its n^{20}_{D} was 1.5345.

Pyrogallol Allyl Diether (II).—The less volatile portion was pyrogallol allyl diether (II); n^{20}_{D} 1.5460. Its yield was 4 g. and there was about 4 cc. of solid residue. The 9 g. of diethers represents a 27% yield.

Pyrolysis of Diether (I).—Two cc. of this ether was heated in a test-tube. At 160° a slight exothermic reaction was noticed but it was heated to 200° to make certain of complete rearrangement. A red, viscous oil remained on cooling. This on distillation in a closed system (165°, 0.001 mm.) yielded about 1 cc. of a thick, yellowish distillate of diallylpyrogallol, $(C_3H_5)_2C_6H(OH)_3$. In the course of time, this changed to a glass. Its n^{20}_{D} value, taken before solidification, was 1.5590.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.80. Found: C, 69.6; H, 7.00.

Pyrogallol Allyl Monoether.—The solution of the crude reaction product in ethyl ether was extracted ten times with water. On evaporation of the ether a red-brown oil remained which solidified after several hours; yield, 10 g. or 60% of the theoretical.

Anal. (Zerewitinoff) Calcd. for $C_3H_5OC_6H_3(OH)_2$: OH, 2.0. Found: OH, 2.07.

The monoether was also prepared directly from pyrogallol and allyl bromide (0.05 mole each) in acetone (100 cc.) without the potassium carbonate. Refluxing was for fourteen hours. The solid reaction product (5 g. or 60%) obtained as before, melted at 62–64°. This material was insoluble in ligroin, cold benzene, carbon tetrachloride and carbon disulfide. It was soluble in ether, acetone, alcohol, sodium hydroxide solution, hot benzene or xylene. It could not be crystallized. Distillation from a closed system (0.02–0.03 mm.) yielded a red oil which set to a glass. When pulverized, this was a yellow solid which melted at 68–70°.

Anal. (Zerewitinoff) Found: OH, 1.94, 1.91.

Data regarding the various allyl ethers are collected in Table II.

Lead Salt.—An excess of lead acetate, dissolved in 33% acetone, was added to a solution of 0.450 g. of the allyl monoether in 10 cc. of acetone. The precipitate of the lead salt which formed was converted to lead sulfate. It was collected on a filter, dissolved in glacial acetic acid, an excess of sulfuric acid added followed by water until a precipitate no longer formed. This lead sulfate was collected and weighed. The yield was 0.664 g. which represents 80% of the theoretical.

Pyrogallol Dimethyl Allyl Triether.—Four grams of the allyl monoether was dissolved in 140 cc. of 15% sodium

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[8] Hickman and Sanford, *J. Phys. Chem.*, **34**, 643 (1930). For convenience in collecting fractions, a multiple rotary receiver (a "pig") was designed with a ground glass joint so that several fractions might be collected by turning the receiver. Usually it was preferable not to use ice as the cooling material in the saucer-shaped roof of the still. Instead, running tap water was used. To prevent overflow, a vertical tube, the bottom of which was at the water level, was attached to a suction pump and this was capable of withdrawing water faster than it was admitted. A steam-bath or a hot air-bath was used to heat the body of the still.

In some cases, the customary mercury vapor pump backed by an oil pump was employed. A preferable set-up, which was adopted in most of the work, consisted of a two-stage mercury vapor pump backed by a water pump. The pressures were read by a McLeod gage.

TABLE II

ALLYL ETHERS OF PYROGALLOL

Ether of pyrogallol	M. p., °C.	n^{20}_D	d^{20}_4	Molecular refraction Calcd.	Molecular refraction Found[a]	Formula	Analyses, % Calcd. C	Analyses, % Calcd. H	Analyses, % Found C		Analyses, % Found H	
Allyl triether	3.5–4	1.5265	1.04	71.7	72.6	$C_{15}H_{18}O_3$	73.17	7.32	73.14		7.59	
Allyl diether (I)	.....	1.5345	1.10	58.2	58.3	$C_{12}H_{14}O_3$	69.9	6.8	69.5	70.0	6.85	6.99
Allyl diether (II)	.....	1.5460	1.13	..	57.7				69.5	69.7	6.80	6.72
Allyl monoether	68–70	....	...	..	..	$C_9H_{10}O_3$	65.2	6.07	65.0		6.67	
Methyl diallyl triether (I)	.....	1.5250	1.059	62.9	63.5	$C_{13}H_{16}O_3$	70.91	7.27	70.94		7.19	
Methyl diallyl triether (II)	.....	1.5280	1.062		63.7				70.86	70.40	7.09	7.31
Dimethyl allyl triether	160–164	....	...	..	..	$C_{11}H_{14}O_3$	68.0	7.30	67.8		7.37	

[a] Lorenz–Lorentz formula.

hydroxide. This was stirred with 20 cc. of methyl sulfate for one and one-half hours and left overnight. The yellow, solid reaction product was crystallized repeatedly from 60% alcohol. Finally, the melting point was 160–164°.

Pyrogallol Methyl Diallyl Triethers.—Four grams of each of the diallyl diethers (I, II) was dissolved in 120 cc. of 20% sodium hydroxide solution and stirred for three hours with an excess of methyl sulfate. The oil which separated was distilled in the Hickman still at 0.30 mm. and 100°. The yields were quantitative.

Rearrangement.—The methyl diallyl triether (II) was heated to 190° by an oil-bath, at which time an exothermic reaction set in. The inside temperature rose to 210°. The mixture was heated at about 200° for two hours with little or no charring. Distillation in the Hickman still (0.005 mm. and 110–115°) gave an almost quantitative yield of liquid which was soluble in alkali and was capable of methylation (by methyl sulfate + alkali) to an alkali-insoluble methyl triether. The liquid was a diallylpyrogallol methyl ether, $(C_3H_5)_2C_6H(OH)_2OCH_3$: n^{20}_D 1.5375, d^{20}_4 1.12, molecular refraction 61.2 (calcd. for $(C_3H_5)_2C_6H(OH)_2OCH_3$, 62.5).

The triether (I), heated similarly, also gave an exothermic reaction at 190° but the product was not worked up for it appeared to have resinified to a black mass.

Hexenyl Derivatives

Pyrogallol Hexenyl Triether.—Fourteen grams of pyrogallol was added to a sodium alcoholate solution (absolute alcohol 200 cc., sodium 4.6 g.). Into this black solution was dropped 32.6 g. of 1-bromo-2-hexene during a half hour. The color changed to brick red and sodium bromide separated. After four hours of refluxing, the solid was filtered off, the alcohol distilled away, the residue taken up in carbon tetrachloride and extracted with dilute sodium hydroxide. The solvent was removed and the residue (9 cc.) fractionally distilled in the Hickman still. Six cubic centimeters of distillate was collected: the first 4 cc., n^{23}_D 1.5045; the next 1 cc., 1.5070; the final 1 cc., 1.5170. The 4-cc. fraction, on redistillation, gave 2 cc. up to 150° (0.0005–0.001 mm.) which was considered to consist chiefly of the triether; n^{23}_D 1.5010, see Table III. The other smaller fractions gave n^{23}_D values of 1.5070, 1.5071, 1.5080.

Dihexenylpyrogallol (I) $(C_6H_{11})_2C_6H(OH)_3$.—The alkaline extract from the triether was acidified, ether extracted and twice distilled in the Hickman still at 200–210° (0.001 mm. or less). The yield of clear, red, viscous liquid, n^{20}_D 1.5225, was 2.5 g. The hexenyl diether (and monoether) may have been present before the distillation, but the high distillation temperature undoubtedly brought about its isomerization to dihexenylpyrogallol (and hexenylpyrogallol).

Dihexenylpyrogallol (II).—This was synthesized from pyrogallol (0.1 mole), potassium carbonate (0.18 mole), dry acetone (200 cc.) and 1-bromo-2-hexene (0.2 mole, added dropwise), the whole refluxed for eight hours, then filtered, concentrated, taken up in benzene and this solution extracted with dilute sodium hydroxide. The material remaining in the benzene was separated into 5-cc. and 3-cc. fractions in the Hickman still at 200°. Redistillation of the first gave: (a) 3 cc., n^{20}_D 1.5312, which on redistillation gave 1 cc. n^{20}_D 1.5314 and 1.7 cc. of n^{20}_D 1.5332; (b) 2 cc., n^{20}_D 1.5360 which on redistillation gave dark red, viscous oils, *viz.*, 1 cc. n^{20}_D 1.5267 and 1 cc. of 1.5350. Fraction (a), by analysis, was fairly pure dihexenylpyrogallol, whereas (b) may have contained some of the monohexenyl analog.

TABLE III

HEXENYL AND HEPTENYL DERIVATIVES

Substance	n^{20}_D	d^{20}_4	Molecular refraction Calcd.	Molecular refraction Found	Formula	Analyses, % Calcd. C	Analyses, % Calcd. H	Analyses, % Found C		Analyses, % Found H	
Pyrogallol hexenyl triether	1.5010 (at 23°)	0.99 (at 23°)	113	110	$C_{24}H_{36}O_3$	77.3	9.75	74.9		9.72	
Dihexenylpyrogallol (I)	1.5225	1.02	87.1	86.3	$C_{18}H_{26}O_3$	74.5	9.03	73.1	72.8	9.04	9.16
Dihexenylpyrogallol (IIa)	1.5332	..		..				74.1		9.13	
Dihexenylpyrogallol (IIb)	1.5350	1.02		88.6				73.5		9.03	
Diheptenylpyrogallol	1.5201	1.00	95.0	96.7	$C_{20}H_{30}O_3$	75.5	9.44	75.9		9.77	
Heptenylpyrogallol	....	..	..	..	$C_{13}H_{18}O_3$	70.3	8.17	70.7		8.45	
Heptenylpyrogallol ethyl triether	1.5082	..	..	..	$C_{19}H_{30}O_3$	74.5	9.87	74.5		10.05	

Care should be taken in handling these materials for during work on the hexenyl compounds the hands of the investigator became poisoned. No remedies appeared to help the itching and burning. The affected parts dried up within three weeks leaving a yellow scar which soon disappeared.

Heptenyl Derivatives

Diheptenylpyrogallol, $(C_7H_{13})_2C_6H(OH)_3$.—This synthesis followed the procedure given for dihexenylpyrogallol (II). From 0.4 mole of pyrogallol and 0.8 mole of 1-bromo-2-heptene there was obtained 100 g. of crude reaction product (soluble in benzene and not extracted by alkali) which gave rise to 10 cc. of distillate in a closed system at 200° (0.001 mm. or less). This 10-cc. portion was fractionated in the Hickman still: (a) 1 cc., $n^{20}_{\rm D}$ 1.4596; (b) 2.8 cc., refractionated into five cuts respectively of $n^{20}_{\rm D}$ 1.4882, 1.5090, 1.5170, 1.5190 and 1.5201; (c) 5.5 cc., $n^{20}_{\rm D}$ 1.5201 and redistilled without change. Analysis of fraction (c) confirmed its identity as diheptenylpyrogallol.

Heptenylpyrogallol.—The alkaline solution from the preparation of diheptenylpyrogallol was acidified and extracted with benzene. Distillation in a closed system (150°, 0.001 mm.) removed the admixed pyrogallol. Further heating to 200° gave rise to a water-insoluble distillate. It was washed with water and redistilled. The heptenylpyrogallol solidified on standing. It weighed 8 g. and melted at 52–53°.

The benzoyl ester of this compound, made by the Schotten–Baumann reaction with benzoyl chloride, was an oil.

Heptenylpyrogallol Ethyl Triether, $C_7H_{13}C_6H_2(OC_2H_5)_3$.—Heptenylpyrogallol (2.4 g.) was ethylated by stirring for one and a half hours with 5.9 g. of ethyl sulfate and 50 cc. of 20% sodium hydroxide. After standing overnight, the oil which separated was distilled twice in the Hickman still; yield, 1.8 cc. The two final fractions collected gave $n^{20}_{\rm D}$ values of 1.5082 and 1.5122. The former predominated and was analyzed. Since heptenylpyrogallol gave rise to this ethyl triether, it excludes the possibility that the former was a heptenyl monoether.

Summary

Pyrogallol alkenyl ethers rearrange into alkenylpyrogallols at temperatures of about 200°.

Various allyl, hexenyl and heptenyl derivatives of pyrogallol are included in this study. Most of the compounds are oils and their low vapor pressure necessitates the use of a molecular still for distillation.

Bactericidal data for several of these compounds are included.

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[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Thermal Data. IV. The Heats of Combustion of Adenine, Hypoxanthine, Guanine, Xanthine, Uric Acid, Allantoin and Alloxan

BY ROBERT D. STIEHLER[1] AND HUGH M. HUFFMAN

In continuation of our plan,[2] of obtaining thermal data on compounds of physiological interest, we present in this paper the combustion data on seven organic compounds containing nitrogen.

Calorimetric Method and Apparatus

The method and apparatus used were essentially those described in a previous communication.[3] Several minor changes have been made which tend to increase the precision of the measurements. We have adopted the constant range method which requires that the initial and final temperatures of all combustions be the same within narrow limits. For convenience in attaining the initial temperature the calorimeter was equipped with an auxiliary heating coil. We have also used exclusively the platinum wire technique[3] in which the mass of the filter paper has been arbitrarily standardized and kept constant within very narrow limits. The accuracy of the mass determinations of the combustible materials was increased by making all weighings on a micro balance sensitive to 0.001 mg. Finally by using a platinum crucible of about 3 g. mass we have decreased the number of combustions in which carbon resulted. The combustions were all made with an oxygen pressure of 30 atm. and with 1 ml. of water in the bomb.

Calibration

Owing to changes in our calorimeter new determinations of its energy equivalent were necessary. These measurements were made at varying intervals throughout the experimental period in order to check the constancy of the system. To determine the energy equivalent we have burned Bureau of Standards benzoic acid standard sample No. 39d. The isothermal heat of com-

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(1) National Research Fellow.

(2) Huffman and Borsook, THIS JOURNAL, **54**, 4297 (1932).

(3) Huffman and Ellis, *ibid.*, **57**, 41 (1935).